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A randomized, controlled trial of high-dose dextromethorphan in facial neuralgias

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Article abstract—*Background:* NMDA glutamate receptor antagonists such as ketamine and dextromethorphan reduce pain in certain neuropathic pain conditions. However, there have been no controlled trials of NMDA antagonists in facial neuralgias. *Methods:* A randomized, double-blind, crossover trial compared 6 weeks of oral dextromethorphan with active placebo (low-dose lorazepam) in 19 patients, stratified into three groups: 11 with facial pain and possible trigeminal neuropathy, five with anesthesia dolorosa, and three with idiopathic trigeminal neuralgia. Dosage was titrated in each patient to the highest level reached without disrupting normal activities. *Results:* Patients completing the trial included 10 with possible trigeminal neuropathy, four with anesthesia dolorosa, and two with trigeminal neuralgia. In patients with possible trigeminal neuropathy and anesthesia dolorosa, dextromethorphan decreased pain by a mean of only 2 to 4%, and these estimates were not significant. Both patients with trigeminal neuralgia had more pain during dextromethorphan treatment than during placebo treatment. Of three patients who demonstrated an analgesic response to dextromethorphan during the main trial, only one repeatedly responded in four subsequent confirmatory drug–placebo crossovers. *Conclusions:* Dextromethorphan shows little or no analgesic efficacy in pain due to possible trigeminal neuropathy and anesthesia dolorosa. Additional trials are necessary to conclusively evaluate the efficacy of NMDA-receptor antagonists in trigeminal neuralgia.

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Pain after nerve injury is associated with changes in dorsal horn neurons, which are modulated by the excitatory neurotransmitter glutamate.¹ Antagonists of the NMDA glutamate receptor such as ketamine and dextromethorphan decrease pain in laboratory models of nerve injury^{2,3} and in clinical neuropathic conditions including diabetic neuropathy, postherpetic neuralgia, spinal cord injury, and complex regional pain syndrome.^{4–11} To our knowledge, there have been no controlled trials of NMDA-receptor antagonists in facial neuralgias including idiopathic trigeminal neuralgia (TN), anesthesia dolorosa, and other conditions related to trigeminal neuropathy.

TN, a relatively uncommon syndrome characterized by brief, excruciating, paroxysmal pains, is caused in part by aberrant blood vessels that compress the trigeminal nerve root.^{12,13} Certain features of TN suggest a functional alteration of second-order brainstem neurons.¹⁴ In one study of 50 patients¹⁵ and another detailed investigation of one patient with TN,¹⁶ investigators inferred that triggering of pain paroxysms occurred through low-threshold, A- β -mediated, afferent stimulation; exhibited patterns of spatial and temporal summation; and may cause pain referred to a site distant from the stimulus, even to another trigeminal division. These stimulus–response features are characteristic of central sensitization¹⁷ and are suppressed in experimental and clinical human pain studies by NMDA antagonists.^{8,9,18,19}

Anesthesia dolorosa is an uncommon complication

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of gasserian ganglion ablation, used to treat TN, characterized by constant burning pain in an area of the face that has been rendered insensate.²⁰ The NMDA antagonist MK-801 was shown to suppress pain behavior following dorsal root ganglionectomy in rats,^{21,22} an experimental model of anesthesia dolorosa, thus providing a rationale for studying the efficacy of NMDA antagonists in this painful condition.

Clinicians encounter many patients with mixed patterns of paroxysmal and continuous pain that do not fit the diagnostic criteria for TN²³ and that are associated with signs and symptoms of trigeminal neuropathy. Diagnostic terms applied to such conditions include atypical facial pain, phantom tooth pain, atypical odontalgia, and atypical facial neuralgia.²⁴ For example, in a recent study,²⁵ 17 patients with atypical facial pain were evaluated with radiologic (CT and MRI), electromyographic, and EEG investigations. Varying degrees of neurophysiologic disturbances, such as abnormal blink and jaw reflexes and abnormal sensory evoked potentials, were observed in 11 patients, suggesting that trigeminal neuropathy may be important in a subset of patients with atypical facial pain. A preliminary, uncontrolled, open-label study suggested analgesic efficacy of the NMDA antagonist ketamine in some patients with neuropathic facial pain.²⁶

Given the lack of controlled trials of NMDA antagonists in facial pain and the above described rationale for their potential utility, the objective of this trial was to evaluate the analgesic efficacy of high-dose dextromethorphan in these three groups of patients with facial neuralgias.

Methods. *Patients.* This study was approved by the Institutional Review Board of the National Institute of Dental and Craniofacial Research. Patients provided informed consent before participating. Patients were recruited nationwide using medical journal advertisements and questionnaires mailed to members of the Trigeminal Neuralgia Association, a patient organization. Three diagnostic strata of patients were recruited. 1) Patients with idiopathic TN (including recurrent TN following invasive peripheral nerve or intracranial procedures) had brief (<2 minutes) paroxysmal pains in the trigeminal distribution; shooting, stabbing or electric-shock-like pain; pain paroxysms elicited by innocuous stimuli; no evidence of peripheral or CNS lesion (except for vascular compression of trigeminal nerve on surgical exploration); and no gross sensory deficit in the trigeminal territory. 2) Patients with anesthesia dolorosa experienced constant pain and sensory loss in the trigeminal distribution following a surgical procedure on the trigeminal nerve. 3) Patients who had pain with features to suggest possible trigeminal neuropathy had at least one of the following: sensory loss, allodynia (pain due to a non-noxious stimulus), continuous burning pain, or paroxysmal shooting pain. The latter two characteristics have been observed more frequently with neuropathic pain than with pain of other etiologies.²⁷

Inclusion criteria were age between 18 and 89 years; daily paroxysms or continuous pain of at least moderate severity unremitting for at least 3 months; a previous trial

of carbamazepine or baclofen (for TN) or a tricyclic antidepressant, an opioid, or gabapentin (for other neuralgias); normal renal and hepatic function; adequate birth control for all women of child-bearing potential; and sufficient cognitive and language skills to complete questionnaires and communicate with nursing staff.

Exclusion criteria were treatment with selective serotonin reuptake inhibitors (because of potential for serotonin syndrome in combination with dextromethorphan²⁸); temporomandibular joint disorder; MS; another condition more painful than the facial neuralgia; major psychiatric disorder; history of substance abuse or alcoholism; major hepatic, renal or cardiac disease; and pregnancy and lactation. Patients taking medication for pain control were asked to discontinue medications of questionable benefit. Apparently efficacious medications could be continued at a stable dose throughout the study.

Neurologic examination included the identification of areas of decreased light touch or pinprick sensation, increased pain to pinprick (hyperalgesia), or pain with stimulation by cotton gauze (allodynia). A psychiatrist (B.S.) screened each patient for major depressive episodes and dysthymic disorder and personality disorder.²⁹ Screening included a general physical examination and standard laboratory tests.

Treatments. Dextromethorphan was compared with an active placebo (low-dose lorazepam) in a randomized, double-blind, two-period, crossover study. Using an active placebo that mimics drug side effects blinds patients more effectively and provides a more rigorous placebo control than an inert placebo.³⁰ The benzodiazepine lorazepam has no analgesic efficacy in postherpetic neuralgia³¹ and has a comparable side-effect profile to that of dextromethorphan.¹⁰ Patients entered a 1-week baseline period, followed by two 6-week drug treatment periods separated and concluded by a 2-week washout period. The treatments, in random order, were dextromethorphan beginning at 120 mg/d in four divided doses titrated to a maximum of 920 mg/d, or lorazepam beginning at 0.24 mg/d in four divided doses titrated to a maximum of 1.84 mg/d.

Bulk dextromethorphan powder was purchased from Ruger Chemical Company (Irvington, NJ) and prepared in 30 and 100 mg capsules by the National Institutes of Health Pharmaceutical Development Service. Matching active placebo capsules of lorazepam (0.06 and 0.2 mg) were prepared.

A study nurse telephoned patients twice weekly to titrate medication dosage and assess pain and side effects. During the first four weeks of each period (titration phase) medication was increased by 30 to 60 mg/d (dextromethorphan) or 0.06 to 0.12 mg/d (lorazepam) twice weekly unless patients reported complete relief, side effects interfering with daily activities, or the maximum daily dose was reached. During weeks 5 and 6 (maintenance phase), the maximal tolerated dose (MTD) was kept constant.

Outcome evaluation. Patients rated pain once daily at bedtime. The primary outcome measure was overall daily pain (described below); secondary measures included intensity of continuous pain and intensity, frequency, and duration of paroxysmal pains. The current intensity of continuous pain was rated by choosing a number from a 0 to 20 box scale upon which 13 verbal pain intensity descriptors³² were interpolated. This scale has been validated

across a broad range of ages in acute and chronic pain and shown to be sensitive to analgesic interventions.³³ The intensity of the worst pain paroxysm experienced over the previous 24-hour period was also rated on the 0 to 20 box scale. Frequency was rated by counting the number of paroxysms that day. Patients estimated the average duration of all paroxysms for that day. Overall daily pain was rated using a 0 to 10 numerical scale. ("Taking into account all the different types of pain you experience, rate your overall facial pain for the past 24 hours. Zero indicates no pain and 10 indicates the most pain imaginable for one day.") This overall daily pain measure, the primary outcome measure, allowed patients to summarize combined ratings of continuous and paroxysmal pain (in patients with a mixed pattern) as well as variable pain throughout the course of a day. At the end of each 6-week treatment period, patients rated global pain relief (5 = complete, 4 = a lot, 3 = moderate, 2 = slight, 1 = no relief, and 0 = pain worse) as compared with the preceding baseline level. During each phone call, patients were asked "Have you experienced any side effects since the last phone call?" Side effects were rated as mild, moderate, or severe. Patients rated the degree to which pain interfered with general activity, mood, walking, normal work, relations with other people, sleep, and enjoyment of life by completing the short-form Brief Pain Inventory (BPI) at baseline and for every week of the study.³⁴ At the end of each treatment period, the patient and the study nurse completed a blinding questionnaire by guessing whether he or she thought the patient was receiving dextromethorphan or placebo.

Confirmatory drug-placebo comparisons. Patients with a pain score favoring dextromethorphan over active placebo by at least one unit on the 0 to 10 overall pain measure entered a confirmatory, "enriched enrollment" study.³⁵ This comparison consisted of four 6-week segments in which the patient took 3 weeks of dextromethorphan and 3 weeks of placebo, assigned in random order. Patients were given the MTD of dextromethorphan from the main trial and the same number of placebo capsules. Evaluation procedures were the same.

Data analysis. We defined the primary outcome variable as the group mean overall daily pain rating for the last 14 days of dextromethorphan treatment compared with the mean for the last 14 days of placebo, using a paired Student's *t*-test. The main analysis considered patients who completed both treatments. In addition, an intent-to-treat analysis included patients receiving at least 1 week of each treatment. Group means for continuous pain intensity, paroxysmal pain intensity, frequency, and duration for the last 14 days of dextromethorphan treatment were compared with placebo using paired Student's *t*-tests.

The required sample size for a crossover study was calculated for each diagnostic group using the formula: $n = (z_{\alpha/2} + z_{\beta})^2(\sigma/\delta)^2$.³⁶ Based on observed variances from TN trials using comparable pain measurement scales,^{37,38} a sample of 12 patients with TN would provide an 80% chance (at an α level of 0.05) of detecting a mean difference in pain between drug and placebo equivalent to 25%. Based on observed variances from neuropathic pain trials,^{39,40} a sample of 11 patients with anesthesia dolorosa, and 11 patients with possible trigeminal neuropathy would

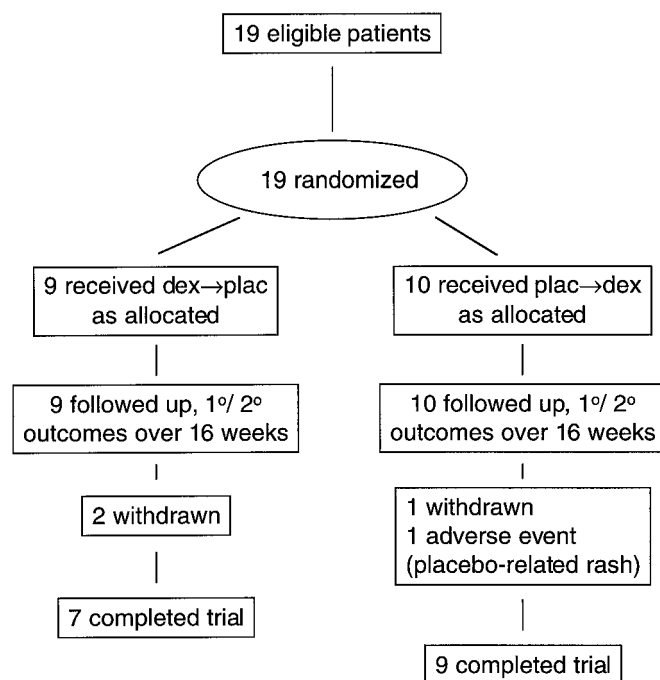


Figure 1. Clinical trial profile describing patient randomization, participant flow, and follow-up.

each provide an 80% chance (at an α level of 0.05) of detecting a mean difference in pain between drug and placebo equivalent to 25%. We set an upper limit of 20 patients for each group and enrolled as many patients as possible between January 1, 1998 and December 31, 1999 so as to complete the study during the fellowship training period of the principal investigator (I.G.). Global pain relief descriptors were converted to a six-point numerical scale and dextromethorphan scores were compared with placebo with the Mann-Whitney *U* test.

Results. Patients. Between January 1, 1998 and December 31, 1999, 174 patient referrals were made to the National Institutes of Health. Of these, 43 patients had medical problems that excluded them (e.g., cardiovascular or liver disease, MS, or a major psychiatric disorder), 32 had an inappropriate diagnosis (e.g., temporomandibular joint dysfunction, postherpetic neuralgia, or headache), 11 had another severe pain problem (e.g., low-back pain, arthritis, or headache), and 69 failed to provide medical records or complete baseline diaries. Nineteen patients (11 with possible trigeminal neuropathy, five with anesthesia dolorosa, and three with TN) were enrolled and randomized (figure 1) and 16 completed both treatments (three men, 13 women; mean age, 53 years; range, 28 to 71 years). The 11 patients with possible trigeminal neuropathy met the following entry criteria suggesting neuropathic pain: three had continuous burning pain, paroxysmal shooting pains, and sensory loss; two had continuous burning pain and paroxysmal shooting pains; two had continuous burning pain and sensory loss; one had continuous burning pain and pinprick hyperalgesia; three had only continuous burning pain; and none had allodynia (table 1). Three patients with possible trigeminal neuropathy (Patients 202, 206, and 215) were diagnosed with mild depression, and all other study patients had normal psychiatric examination results. One patient with TN dropped out

Table 1 Clinical characteristics of patients with facial neuralgia at the time of study enrollment

Patient no.	Age	Sex	Pain duration, y	Pain location	Pain pattern	Sensory examination*	Previous procedures
Possible trigeminal neuropathy							
201	39	F	2	L-V2	C	Hypoesthesia (PP+LT)	—
202	48	F	7	L-V1	C+P	Hypoesthesia (PP+LT), ↓ corneal	—
204	51	F	3	L-V2	C	Hypoesthesia (LT)	—
206	60	F	9	L-V1, V2, V3	C+P	—	—
207	56	F	17	L-V2	C	—	MVD
208	28	M	6	R-V1, V2	C+P	—	GA, MVD
209	47	F	2	L-V1, V2, V3	C+P	Hypoesthesia (PP+LT)	MVD
212	59	F	6	R-V2	C	—	—
214	59	F	7	R-V2, L-V2	C	—	—
215	58	M	10	L-V1, V2	C	PP hyperalgesia	GA
217	37	F	3	L-V1, V2	C+P	Hypoesthesia (PP)	—
Anesthesia dolorosa							
203	62	F	2	L-V1, V2, V3	C+P	Hypoesthesia (PP+LT), ↓ corneal reflexes	†
205	66	F	6	L-V2, V3	C	Hypoesthesia (PP+LT)	GA, DREZ
210	63	M	5	L-V2, V3	C	Hypoesthesia (PP+LT)	GA
211	43	F	7	R-V1, V2, V3	C+P	Hypoesthesia (PP+LT)	GA
213	71	M	18	R-V2, V3	C	Hypoesthesia (PP+LT)	GA, MVD
Idiopathic trigeminal neuralgia							
216	50	F	3	L-V2, V3	P	Hypoesthesia (PP+LT), trigger points	—
218	71	M	11	R-V2, V3	P	Hypoesthesia, ↓ corneal reflexes, trigger points	GA
219	58	F	12	R-V2	P	Trigger points	—

* In all patients, noted sensory abnormalities were observed within the painful dermatomes.

† Excision of a trigeminal nerve Schwann cell tumor.

V1 = ophthalmic division; V2 = maxillary division; V3 = mandibular division; P = paroxysmal; C = continuous; C+P = mixed pattern; PP = pinprick; LT = light touch; GA = gasserian ganglion ablation; MVD = microvascular decompression; DREZ = dorsal root entry zone lesion.

after 22 days of the first treatment period (dextromethorphan) to undergo a gasserian ganglion ablation. A second patient (with anesthesia dolorosa) dropped out after 26 days of the first treatment period (dextromethorphan) because of intolerable sedation. A third patient, with possible trigeminal neuropathy, was discontinued from the study after 1 day of the first treatment period (active placebo) because of a new skin rash. The mean duration of pain in the 16 patients who completed both treatments was 7 years (range, 2 to 18 years) (see table 1).

Facial pain with possible trigeminal neuropathy. For patients with facial pain with possible trigeminal neuropathy, the mean MTD was 357 mg/d for dextromethorphan and 1.2 mg/d for the active placebo (lorazepam). In the last 2 weeks of the 6-week treatment period, there was slightly less pain while receiving dextromethorphan than placebo (table 2). As measured by the 0 to 10 overall daily pain scale, pain during dextromethorphan treatment decreased by a mean of 4% (95% CI, 35% decrease to 27% increase; $p = 0.81$). Global pain relief ratings were similar for the

two treatments (dextromethorphan: a lot three, moderate one, slight four, and none two [mean 2.5, where 2 = slight and 3 = moderate relief]; placebo: a lot two, moderate two, slight three, none two, and pain worse one [mean 2.2, in which 2 = slight and 3 = moderate relief]). Figure 2, in which each open circle represents a patient with possible trigeminal neuropathy, shows no apparent reduction in overall daily pain, continuous pain intensity, or paroxysm frequency, intensity, or duration.

Three patients (Patients 201, 202, and 209) were enrolled in the confirmatory study. There were no apparent differences between the three dextromethorphan responders and the nonresponders with regard to duration of disease, concomitant medications, pain pattern, or sensory findings.

Anesthesia dolorosa. For patients with anesthesia dolorosa, the mean MTD was 178 mg/d for dextromethorphan and 1 mg/d for the active placebo (lorazepam). In the last 2 weeks of the 6-week treatment period, there was slightly less pain while receiving dextromethorphan than placebo

Table 2 Concurrent medications, study drug doses, pain ratings, and Brief Pain Inventory (BPI) scores during treatment with dextromethorphan and active placebo

Patient no.	Concurrent medications	MTD (mg/d)		Overall daily pain (0–10)*		BPI score (0–70)	
		Dex	Plac	Dex	Plac	Dex	Plac
Possible trigeminal neuropathy							
201	Op	680	1.04	4.8	7.1	11.0	32.0
202	Op, TCA	400	0.4	2.5	6.7	14.0	50.0
204	—	240	0.76	4.8	0	2.5	0.0
206	Op	210	0.52	5.1	4.3	19.0	17.0
207	TCA, Bac	460	1.84	4.9	3.7	8.5	16.0
208	Op	640	1.84	8.1	8.7	44.0	66.5
209	—	520	1.84	0.9	4.5	0.5	9.5
212	—	150	1.16	3.8	2	16.0	15.0
214	Op, TCA, GBP	120	1.84	7.4	7.4	21.0	20.5
215	Op	150	0.3	9.9	10	36.0	46.5
217†	Op, TCA, GBP	—	—	—	—	—	—
Anesthesia dolorosa							
203	TCA	120	0.52	6.4	6.1	30.0	34.8
205	TCA, GBP	320	0.4	6.9	7.3	30.0	32.0
210††	TCA	—	—	—	—	—	—
211	Op, TCA, GBP, Bac	90	1.84	6.4	6.7	36.0	38.0
213	Op, TCA, GBP	180	1.04	4.9	4.9	33.0	27.0
Idiopathic trigeminal neuralgia							
216	CBZ	580	1.16	7	3.4	19.0	1.0
218§	Bac, Phe	—	—	—	—	—	—
219	TCA, CBZ	640	1.84	5	4.2	12.0	8.5

BPI score: total of 7 items from the BPI assessing the degree of pain-related interference with normal activities (high scores indicate high level of pain-related interference).

* Data means are from last 2 weeks of each respective treatment period.

† Discontinued from study after 1 day of first treatment period (plac) because of new onset skin rash.

‡ Dropped out after 26 days of first treatment period (dex) because of intolerable sedation.

§ Dropped out after 22 days of the first treatment period (dex) because of pain exacerbation and pursued gasserian ganglion ablation.

Bac = baclofen; Phe = phenytoin; CBZ = carbamazepine; TCA = tricyclic antidepressant; GBP = gabapentin; Op = opioid; Dex = dextromethorphan; Plac = placebo (lorazepam).

(see table 2). As measured by the 0 to 10 overall daily pain scale, pain during dextromethorphan treatment decreased by a mean of 2% (95% CI, 7% decrease to 4% increase; $p = 0.64$). Global pain relief ratings were similar for the two treatments (dextromethorphan: moderate one, slight two, and none one; placebo: slight one, and none three). Figure 2, in which each open diamond represents a patient with anesthesia dolorosa, shows no apparent reduction in overall daily pain, continuous pain intensity, or paroxysm frequency, intensity, or duration.

Idiopathic trigeminal neuralgia. The MTD for the patients with idiopathic trigeminal neuralgia (Patients 216 and 219) were 580 mg/d and 640 mg/d for dextromethorphan and 1.16 mg/d and 1.84 mg/d for active placebo (lorazepam). In the last 2 weeks of the 6-week treatment period, there was less pain for both patients while receiving the placebo than dextromethorphan (see table 2). As measured by the 0 to 10 overall daily pain scale, pain for

Patients 216 and 219 during dextromethorphan treatment increased by a mean of 37% (95% CI, 10% decrease to 84% increase; $p = 0.36$). Global pain relief ratings for Patients 216 and 219 at the end of each treatment period for dextromethorphan were no relief and moderate relief, and for placebo, moderate relief and slight relief. Figure 2, in which each open square represents a patient with trigeminal neuralgia, shows no reduction by dextromethorphan in overall daily pain or paroxysm frequency, intensity, or duration.

Effect of treatment on pain-related interference (all study groups). A positive correlation was observed between dextromethorphan-related changes in pain-related interference and changes in overall daily pain (see table 2; $r = 0.75$; $F = 16.6$; $p = 0.0013$).

Adverse effects (all study groups). All 16 patients in the study reported moderate or severe side effects during dose titration with dextromethorphan, 10 during titration with active placebo. Side effects due to dextromethorphan

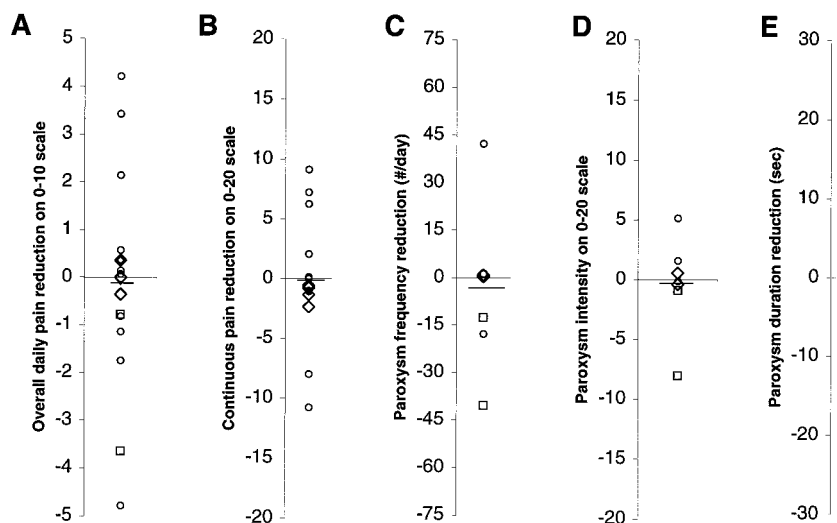


Figure 2. Reduction of overall daily, continuous, and paroxysmal pain by dextromethorphan for each patient, calculated as the difference between means over the last 2 weeks of placebo treatment and the last 2 weeks of dextromethorphan treatment. Positive values indicate reduction of pain by dextromethorphan relative to placebo. The heavy horizontal line indicates the mean reduction for each parameter. Considering patients from all study groups who experienced continuous and paroxysmal pain, dextromethorphan treatment did not significantly reduce overall daily pain (A), continuous pain intensity (B), or paroxysm frequency (C), intensity (D), or duration (E) in

comparison with placebo treatment in the last 2 weeks of the 6-week treatment period. Circles = possible trigeminal neuropathy; diamonds = anesthesia dolorosa; squares = idiopathic trigeminal neuralgia.

and lorazepam treatment were dose-related and reversible. During maintenance treatment at the MTD, six patients reported side effects with dextromethorphan and seven with lorazepam. The most common side effect with dextromethorphan was cognitive impairment; with lorazepam it was fatigue or sedation. During dose titration, the occurrence of cognitive impairment, dizziness or ataxia, and any side effect was more frequent with dextromethorphan than with lorazepam ($p < 0.01$; χ^2 analysis; data not shown; for more information, please visit the *Neurology* Web site at www.neurology.org). However, there were no significant differences in side effects between dextromethorphan and lorazepam during maintenance at MTD.

Blinding (all study groups). Of the 16 patients, nine correctly and seven incorrectly guessed their treatment after the first period (NS; χ^2 analysis); following the second period, 10 correctly and six incorrectly guessed their treatment (NS). After the first treatment period, the study nurse correctly guessed the treatment nine times and incorrectly guessed seven times (NS); after the second period, the study nurse correctly guessed the treatment 10 times and incorrectly guessed six times (NS).

Confirmatory study and follow-up. Three patients entered the four-crossover confirmatory study (Patients 201, 202, and 209), all having possible trigeminal neuropathy. Patient 201 completed only two crossover pairs and Patient 202 showed an analgesic response in only two of the four crossovers (data not shown; for more information, please visit the *Neurology* Web site at www.neurology.org). Patient 209 responded consistently during all four crossovers and is currently on open-label treatment with dextromethorphan.

Discussion. These data suggest little or no efficacy of high-dose dextromethorphan in facial neuralgias. It is unlikely that these apparently negative results were due to chance, insensitivity of measurement scales, or bias. Data measuring treatment-related changes in pain-related interference with daily activities, using the short-form BPI showed a significant, positive correlation with changes in overall daily pain. This suggests that study patients were consistent when completing pain diaries and interference

questionnaires and, furthermore, that the BPI may be a sensitive measure of functional improvement in analgesic trials. Finally, our blinding questionnaire data indicate that neither patients nor study nurses were able to identify dextromethorphan more frequently than expected due to random chance, suggesting that low-dose lorazepam is an effective placebo control and that the study was well blinded.

Only two patients with TN completed the study and although both had more pain during dextromethorphan treatment, both exhibited considerable fluctuations in pain. Thus, more data are needed to conclusively evaluate the efficacy of NMDA-receptor antagonists in TN. It should be noted that one patient with possible trigeminal neuropathy demonstrated an analgesic response to dextromethorphan during the main trial that was subsequently replicated in all four confirmatory drug-placebo crossovers. Although this may be a true response to dextromethorphan, we cannot rule out a powerful placebo effect or chance finding.

Together with the observation of selective efficacy of dextromethorphan in painful diabetic neuropathy but not in postherpetic neuralgia,^{4,10} these results emphasize the limitations of dextromethorphan in the treatment of neuropathic pain. A major problem may be the poor therapeutic ratio of available NMDA antagonists. For example, virtually any pain can be completely relieved with IV ketamine,^{5,9,41} but this may be at the expense of intolerable adverse effects. A study that measured brain dextromethorphan concentrations in neurosurgical patients⁴² demonstrated that preoperative oral administration of dextromethorphan (1,400 mg/d) resulted in tissue concentrations that just began to approach the range needed for neuroprotection in animal models. Because our trials are meant to emulate analgesic use for chronic pain management, ambulatory titration to MTD seeks to determine the highest possible dose without impairing patient function. Our observed

MTD of 340 to 400 mg/d for dextromethorphan^{4,10} likely provide only limited blockade of NMDA receptors and may partly explain the lack of efficacy in facial neuralgias.

Thus, future studies of NMDA-receptor antagonists in the treatment of facial neuralgias as well as other neuropathic pain conditions should evaluate the efficacy of agents with a better therapeutic ratio. For example, investigational NR_{2B} subunit-selective NMDA receptor antagonists such as CP-101,606 and Ro 25-6981 have demonstrated analgesic effects in animal pain models at doses that do not cause any impairment of motor coordination.^{43,44} The clinical development of these and other similar NMDA-receptor antagonists may provide antineuralgic drugs that are superior to current therapies.

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Lack of efficacy of riluzole in the treatment of peripheral neuropathic pain conditions

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Article abstract—*Objective:* To assess the efficacy, tolerability, and safety of riluzole in the treatment of peripheral neuropathic pain conditions. *Background:* Both basic and clinical research has demonstrated that drugs with sodium channel and NMDA antagonism can be effective in alleviating neuropathic pain. Riluzole, a drug currently used for treatment of ALS, possesses these properties. It was hypothesized that riluzole would be effective in reducing the pain in subjects with peripheral neuropathic pain. *Methods:* Two randomized, placebo-controlled, crossover studies were performed at two sites. Study 1 compared 100 mg/day of riluzole (the currently recommended dosage for treatment of ALS) versus placebo, and Study 2 compared 200 mg/day of riluzole versus placebo. Each treatment phase (both studies) was 2 weeks long, separated by 2-week wash-out periods. Outcome measures included change in the score on a 100-mm pain intensity visual analog scale, the Neuropathic Pain Scale, allodynia, hyperalgesia, and preference for study treatment phase. *Results:* Twenty-two subjects completed Study 1, and 21 subjects completed Study 2. Four subjects (two from each study) discontinued the study because of intolerable side effects. No statistical difference was found for any study outcome measure between riluzole and placebo for either study. In Study 1, pain intensity was more likely to increase than decrease with riluzole (mean treatment difference 8.7 mm; 95% CI -19.5 to +2.1 mm). In Study 2, very slight pain reduction was observed with riluzole compared with placebo (mean treatment difference 1.4 mm; 95% CI -5.1 to +8.0 mm). In both studies, the majority of subjects chose "no change" in pain on the category relief scale after placebo and riluzole treatment phases. On study completion, no treatment preference was reported by 76% of the subjects in Study 1 and by 61% of the subjects in Study 2. *Conclusions:* Doses of riluzole at (100 mg) or above (200 mg) those used for the treatment of ALS were not effective in alleviating peripheral neuropathic pain.

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Animal models have demonstrated several potential pain mechanisms underlying the generation and maintenance of neuropathic pain.¹ These mechanisms include ectopic impulse generation associated with an upregulation of sodium channels² and central sensitization dependent on excitatory amino acid receptor activity.³ In fact, several drug classes that have been shown in randomized controlled trials to be of benefit in neuropathic pain are believed to act, at least in part, via sodium channel blockade; among

these are tricyclic antidepressants such as amitriptyline, anticonvulsants such as carbamazepine and phenytoin, and local anesthetic agents such as lidocaine and mexiletine.⁴ Studies have reported an improvement of animal pain behavioral measures after administration of NMDA antagonists such as dextromethorphan and MK-801.⁵ Additionally, a small controlled clinical study has observed efficacy of dextromethorphan.⁶

Thus, a drug that blocks sodium channels and has

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